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PATENT & TRADEMARK OFFICE

Attorney Docket No. UAB-14202/22

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Robert P. Kimberly

Serial No.: 09/744,373 — Group Art Unit: 1634

Filing Date: May 16, 2001 — Examiner: Sally A. Sakelaris

For: GENETIC POLYMORPHISM IN THE RECEPTOR FOR IgA

DECLARATION OF ROBERT P. KIMBERLY, M.D. OFFERED UNDER 37 CFR 1.132

I, Robert P. Kimberly, M.D., hereby declare as follows:

1. I am Director of the Division of Clinical Immunology and Rheumatology and Director of the UAB Arthritis and Musculoskeletal Center (AMC). I am a rheumatologist and immunologist with expertise in autoimmune disease including systemic lupus erythematosus, systemic vasculitis and rheumatoid arthritis. I am currently the Principal Investigator of the UAB Specialized Center of Research in the Genetics of SLE, a unique consortium of seven academic centers. I am co-leader, with Dr. Richard Kaslow, of the Genetics and Functional Genomics workgroup of the AMC. I have served on, and chaired, the Center for Scientific Review GMA-1 Study Section, various review groups for NIAMS Multipurpose Arthritis and Musculoskeletal Diseases Centers, for NIAMS Rheumatic Disease Core Centers, for assorted Program Projects (NIAMS, NIAID, NIDDK), and GCRC review groups. I have also chaired the Peer Review Council of the National Arthritis Foundation in 1999 and 2000, chaired the Medical and Scientific Committee of the National Arthritis Foundation and was a member of the Arthritis Foundation's Blue Ribbon Committee on Research. I was also an invited member of the NIAMS

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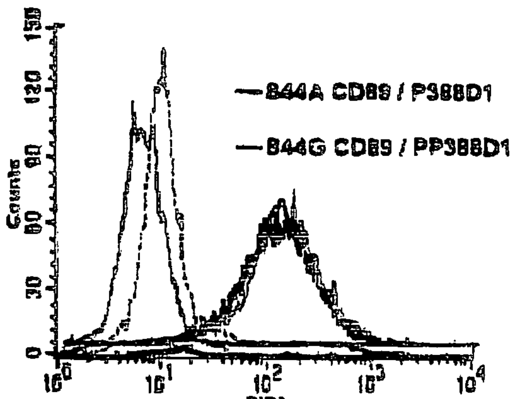
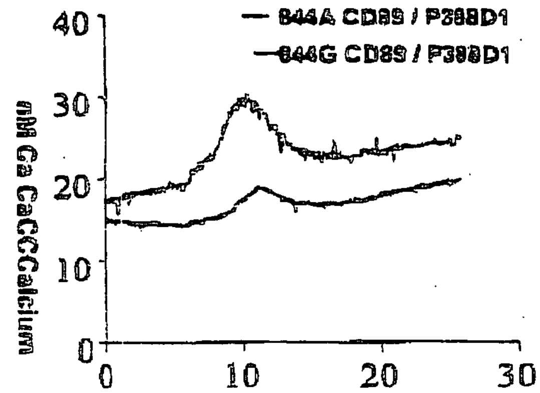
Centers Working Group I (1996), was a contributing member to the NIAID Task Force on Immunology XI (1997) and served on the NIAMS Scientific Program Planning Retreat meeting (2001). I have served on multiple national committees for the American College of Rheumatology and am a member of the American Society for Clinical Investigation and the Association of American Physicians. I have also served on the Editorial Boards of Arthritis and Rheumatism, Journal of Clinical Investigation, and Genes and Immunity.

2. I am the inventor of the above-identified patent application, U.S. Application Serial No. 09/744,373 ("the Application") and have read the Office Action dated May 7, 2004 ("the Office Action").

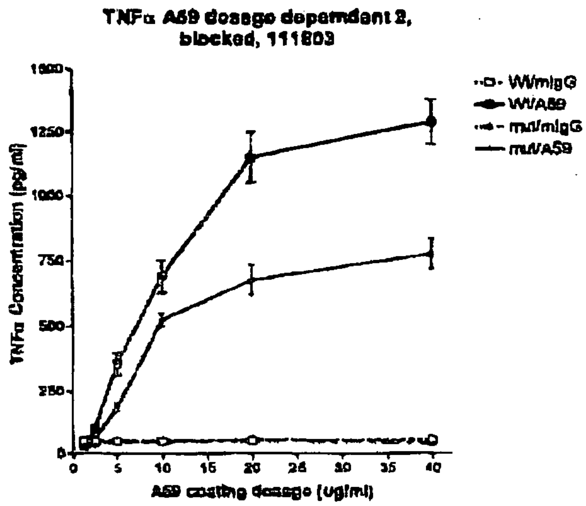
3. I understand that pending claims 1-21, 26-30, and 36-46 of the Application have been rejected under 35 U.S.C. §112, first paragraph, for failing to teach the correlation of the single nucleotide polymorphisms (SNPs) in the FcαRI receptor and cellular susceptibility to a disease. I intend to demonstrate that the FcαRI cellular function varies with SNPs and that the cellular function of such cells correlates with disease states.

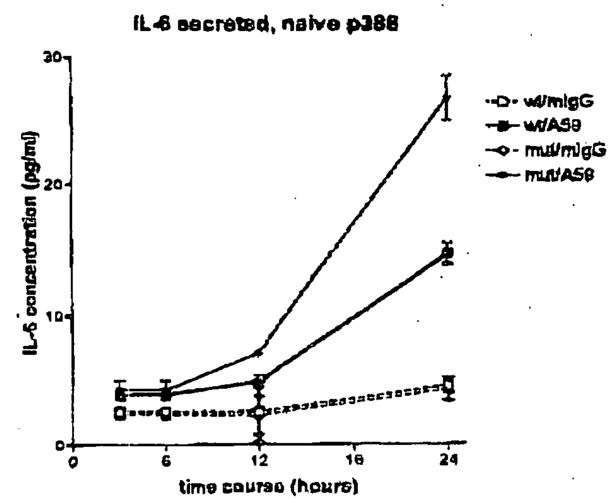
4. My work with respect to identifying single nucleotide polymorphs within the CD89 receptor as detailed in this patent application demonstrates that the function of CD89 expressing cells varies with the allelic form of the receptor that is expressed.. Data generated consistent with methodology detailed in Example 25 of the patent application is provided below for stable transfectants of human CD89 in the mouse myeloid cell line, P388D1, where expression numbers of the two different allelic forms of CD89 were identical but the functional capacity of the base 844A allelic form to initiate an intracellular calcium flux was greater relative to the 844G base (corresponding to changing amino acid codon 248 from serine to glycine in the cytoplasmic region of the CD89 receptor).

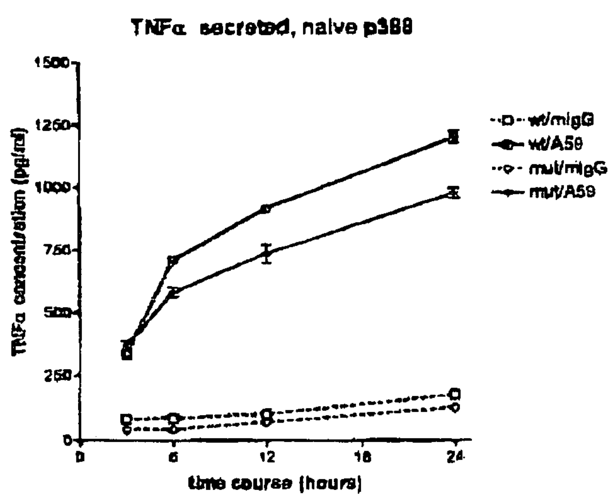


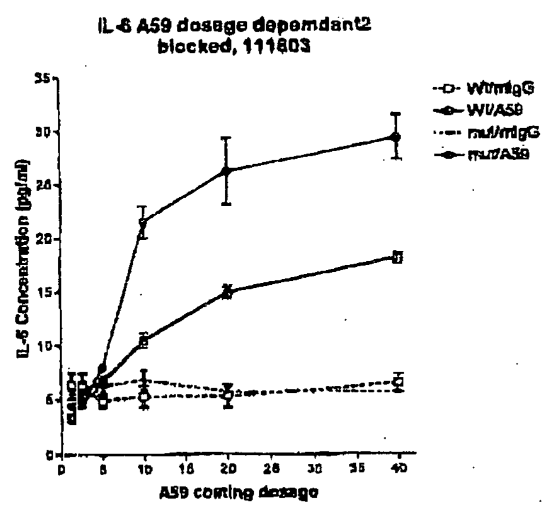


Cytokine assays in P388D1 cells stably transfected were assayed for cytokine production of IL-6 and TNFα according to the procedure of Example 17 of the patent application. The 844G(Gly^{248}) allele of CD89 is shown in the following graphs to clearly release more IL-6 and less TNFα upon binding stimulation of the CD89 receptor, as compared to a like number of 844A allele containing receptors.

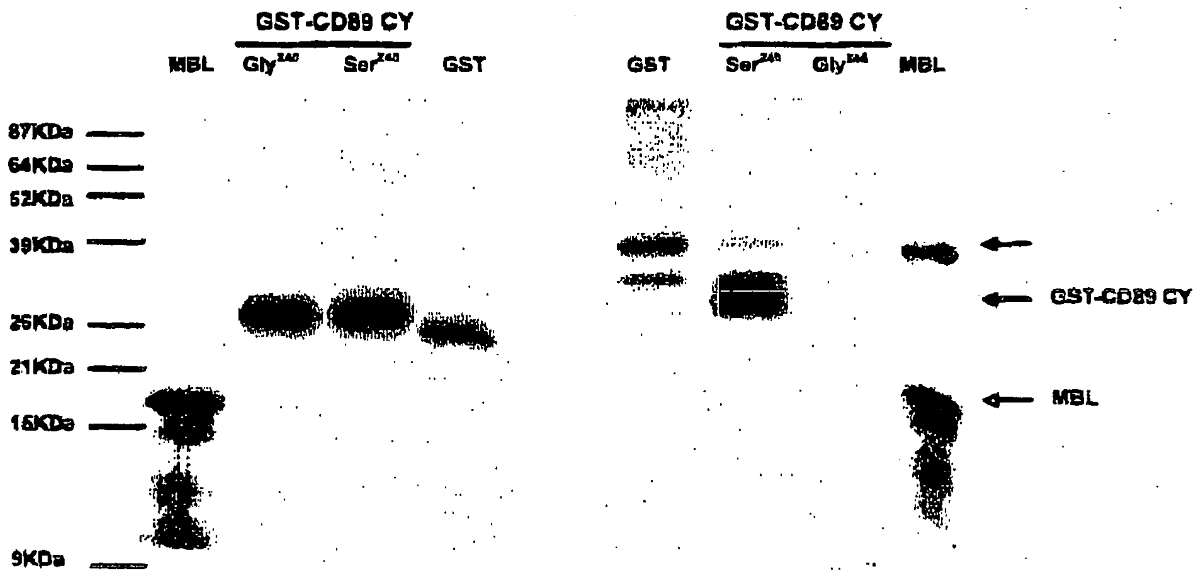








GST-CD89 fusion proteins were also generated according to Example 8 of the patent application. The ability of the resulting fusion protein to be phosphorylated is dictated by the single nucleotide polymorphism.



A, staining gel B, radioactive gel

5. Based on the above experimental data, I believe it is perfectly clear that single nucleotide polymorphisms in the CD89 receptor profoundly affect the intracellular signaling, ion flux, cytokine production, and phosphorylation reactions within a cell expressing the CD89 receptor. The data I provided is but a small portion of the cellular function changes noted with this SNP. Comparable data exists for the other SNPs currently recited in the claims.

6. The correlation between CD89 induced cellular function has long been known and predates my invention. In support of this statement a number of publication abstracts are provided that detail a correlation between various diseases and CD89 induced cellular functions including cytokine production and calcium flux. The attached abstracts include:

Hughes et al. "Calcium channel blockade inhibits release of TNF alpha and improves survival in a rat model of acute pancreatitis." *Pancreas*. 1996 Jul; 13(1):22-8.

Badolato et al. "Role of cytokines, acute-phase proteins, and chemokines in the progression of rheumatoid arthritis." *Semin Arthritis Rheum*. 1996 Oct; 26(2):526-38.

Lo et al. "Calcium and calmodulin regulate lipopolysaccharide-induced alveolar macrophage production of tumor necrosis factor and procoagulant activity." *Arch Surg.* 1996 Jan; 131(1):44-50.

Sautner et al. "Tumour necrosis factor-alpha and interleukin-6: early indicator of bacterial infection after human orthotopic liver transplantation." *Eur J Surg.* 1995 Feb; 161(2):97-101.

Ettehadi et al. "Elevated tumour necrosis factor-alpha (TNF-alpha) biological activity in psoriatic skin lesions." *Clin Exp Immunol.* 1994 Apr; 96(1):146-51.

7. With reference to appended Table 1, the distribution of the single nucleotide polymorphism found at CD89 codon 844 is associated with an individual's cellular susceptibility to SLE. CD89 SNP 844 is responsible for changing amino acid codon 248 from serine to glycine in the cytoplasmic tail region of the CD89 receptor. Referring now to Table 1, four populations were identified as to Caucasian or African American and whether the individual is healthy or suffers from SLE. The number of individuals in each population is noted by the variable "n". The genotype of each individual in each of the four different populations detailed in Table 1 was genotyped with respect to CD89 SNP 844, and the allelic frequency of A and G are noted for each of these groups. As Table 1 makes clear, the allelic frequencies are significantly different for Caucasians in that more G is noted in SLE patients ($p<0.05$) and the difference approaches significance within the African American study populations ($0.05<p<0.10$).

Even through genotyping of only the CD89 SNP 844, it is apparent that SLE patients have cellular function differences as a result of the amino acid change at codon 248. (See the above data and Badolato et al. *Semin Arthritis Rheum.* 1996; 26(2) 526-38.)

Within a particular ethnic population, genotyping of an individual for CD89 single nucleotide polymorphisms is a valuable treatment tool. The data found in Table 1, even though from a complex multivariable system, also makes clear that the greater the number of copies of

CD89 having glycine at amino acid codon 248 are cumulatively more likely to suffer the effects of SLE. The relative percentages of sufferers having "AG" and "GG" genotypes bears out this conclusion.

The strong correlation between the G allelic frequency and SLE, especially for a Caucasian patient population, based on genotyping only a single nucleotide polymorphism at CD89 (844) has important clinical implications in that, for instance, an individual who has a genotype CD89 844 GG can be treated from a standpoint of having fully functional circulating IgA present in sufficient quantity in that the problem lies in the CD89 receptor. In such an instance, treatment protocols aimed at modifying an individual's IgA levels are expected to be not only ineffective but likely deleterious. Additionally, an individual genotyped as being GG at CD89-844 who does not manifest SLE symptoms can be counseled and make lifestyle modifications, as well as undergo additional monitoring to catch the disease at an early stage of clinical manifestation.

As noted in the specification, periodontal disease is a prototypical autoimmune disease correlated with CD89 receptor mediated cellular function. Taken together, the genotyping of an individual and the correlation of the genetic data with disease susceptibility are submitted to be clearly taught to one skilled in the art such as myself through a reading of the application specification.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 9/20/04

Robert P. Kimberly, M.D.

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Distribution of CD89 SNP 844 AGC(Ser^{248}) / GGC(Gly^{248}) in four different populations

	Caucasian SLE Patients n = 52	Caucasian Controls n = 68	AA SLE Patients n = 54	AA Non-SLE Controls n = 64
Genotype No. of Subjects (% of Group)				
AA	32 (61%)	51 (75%)	21 (39%)	32 (50%)
AG	16 (31%)	16 (24%)	26 (48%)	32 (45%)
GG	4 (8%)	1 (1%)	7 (13%)	3 (5%)
Allelic Frequency				
A	0.77	0.87	0.63	0.73
G	0.23	0.13	0.37	0.27

Allelic frequency of Gly^{248} (SNP 844G) in SLE patients is significantly higher than that in non SLE populations

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